

predicators of OS: age, gender, diagnosis, KPS, stem cell source, LVEF, resting HR and O2sat, reaching target HR, DLCOcorr and FEV1. For allogeneic BMT, multivariate analysis demonstrated age < 40 years (RR = 0.37,  $p = 0.03$ ) and higher FEV1 (RR = 0.98,  $p = 0.02$ ) had a decreased risk and KPS  $\leq 80$  (RR = 3.19,  $p = 0.01$ ) had increased risk of death. For autologous BMT, multivariate analysis demonstrated significantly decreased risk of death for higher baseline HR (RR = 0.95,  $p = 0.002$ ), baseline O2sat (RR = 0.69,  $p = 0.01$ ), LVEF (RR = 0.91,  $p = 0.04$ ) and DLCOcorr (RR = 0.97,  $p = 0.02$ ). Early OS may be predicted using simple measures of cardiac, pulmonary and exercise functions pre-BMT.

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### PRE-TRANSPLANT CLONAL CYTOGENETIC ABNORMALITIES IN STEM CELLS USED FOR AUTOLOGOUS STEM CELL TRANSPLANT FOR RELAPSED NON-HODGKIN LYMPHOMA IS A PREDICTOR OF RELAPSE

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Autologous stem cell transplant is used for chemotherapy sensitive relapsed Non-Hodgkin Lymphoma (NHL). Patients who receive an autologous stem cell transplant after high dose chemotherapy for relapsed NHL have significantly superior survival compared to those receiving conventional chemotherapy. Relapsed patients who achieve a second remission are treated with myeloablative chemotherapy followed by autologous stem cell transplant. These patients can achieve 5-year event free survival close to 50% and 5-year overall survival of greater than 50%. We performed a retrospective analysis of our center's transplant data and reviewed pre-transplant cytogenetic analysis on the patient's collected stem cells. 259 patients underwent autologous stem cell transplant from 1998 through 2007 for relapsed NHL. Cytogenetic evaluations of the patient's pre-transplant stem cells had been done to look for evidence of MDS or characteristics of their lymphoma. Clonal cytogenetic abnormalities were found in 12 of the 259 patients. Two of these patients died within 45 days of transplant without evidence of relapse. One from infection and a second from non-treatment related causes. Nine of the remaining 11 (81%) patients with clonal cytogenetic abnormalities have relapsed and died. All patients relapsed with their original lymphoma. The cytogenetic abnormalities were varied. Out of the 9 relapses, 3 had cytogenetic abnormalities in the stem cells that are associated with lymphoma, 2 that are associated with AML, 1 that is associated with MDS, and 2 were abnormalities whose significance was unknown. In one patient cytogenetic changes of the original lymphoma were identified. The patients that had clonal cytogenetic abnormalities in their collected stem cells had an 81% relapse rate as opposed to 30% in the patients whose stem cells had a normal karyotype. Our findings show that cytogenetic changes in the collected stem cells are associated with a higher rate of lymphoma relapse.

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### AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) WITH A PCR-NEGATIVE GRAFT WAS ASSOCIATED WITH A FAVORABLE OUTCOME FOR CORE-BINDING-FACTOR ACUTE MYELOID LEUKEMIA (CBF-AML)

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Although core binding factor acute myeloid leukemia (CBF-AML) is generally considered to be a low-risk form of AML, the survival rate is still 50–60%. To evaluate the effectiveness of autologous stem cell transplantation (ASCT) with a PCR-negative graft, we analyzed a series of consecutive CBF-AML patients. Between 1997 and 2006, 18 patients aged less than 60 years were referred under a diagnosis of CBF-AML. Peripheral blood stem cells (PBSC) were collected after a second or further course of post-remission therapy. When more than  $2.0 \times 10^6/\text{kg}$  CD34-positive cells with minimal residual disease (MRD) undetectable by nested PCR had been collected, ASCT was performed with busulfan, etoposide and cytarabine combined with granulocyte colony-stimulating factor. Event-free survival (EFS) and complications of ASCT were then as-

sessed. Fourteen of the 18 patients received ASCT. The median observation period was 4.4 years. The 5-year EFS was 93% for ASCT patients, despite the presence of adverse factors. In 8 of 10 patients who had detectable MRD in the bone marrow before ASCT, MRD became undetectable after ASCT. Neutrophils recovered promptly within 2 weeks, but platelets recovered relatively slowly. Half of the patients suffered from varicella zoster virus infection. Although one case of myelodysplastic syndrome occurred, there was no case of relapse. ASCT with a PCR-negative graft was associated with excellent EFS. For patients with CBF-AML, especially with adverse factors or remnant MRD in the bone marrow, this strategy is the treatment of choice.

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### FEBRILE REACTIONS OCCURRING WITH SECOND CYCLE OF HIGH DOSE MELPHALAN AND STEM CELL TRANSPLANTATION IN PATIENTS WITH AL AMYLOIDOSIS: A "MELPHALAN RECALL" REACTION

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Systemic AL amyloidosis is a clonal plasma cell disease characterized by the wide spread deposition of amyloid fibrils into tissues and organs. Treatment for this disease is directed towards reducing the production of amyloidogenic monoclonal light chains by attacking the underlying plasma cell dyscrasia. Aggressive treatment with high dose intravenous melphalan followed by autologous stem cell transplantation (HDM/SCT) is effective in inducing hematologic and clinical remissions and in extending survival. Tandem cycles of HDM/SCT have been shown to increase hematologic complete response (HCR) rates in patients with AL amyloidosis. Between April 1994 and July 2008, 57 patients with AL amyloidosis at Boston University medical center were treated with a second cycle of HDM/SCT after failing to achieve a HCR following a first transplantation. Eleven of 57 patients (19%) treated with tandem transplantation developed a high fever 12–24 hours following melphalan administration. Other clinical features noted in some of the patients include hypotension, acute renal failure, and skin rash. Among the 11 patients described, there were 7 men and 4 women. The average age was 53.5 years (range 41–60). The average peak temperature of the 11 patients was 39.1°C (range, 38.1–39.4°C). All patients experienced resolution of fever within 24–48 hours. Six of the 11 patients developed a rash and 5 developed hypotension that was responsive to intravenous fluids or pressors when indicated. Two of the patients developed acute renal failure that improved following resolution of the fever. In all 11 patients, workup for an infectious etiology of fever was negative. One of the 11 patients described, had cytokine measurements before, during and after the febrile reaction. The concentration of several pro-inflammatory as well as anti-inflammatory cytokines increased significantly. IL-6, a classic endogenous, pyrogenic cytokine, increased 10 fold with this reaction demonstrating a clear physiologic response correlating with the clinical findings. We conclude that an unusual febrile reaction mediated by pyrogenic cytokines can occur in patients with AL amyloidosis exposed to a second cycle of high dose melphalan. While this reaction has not been observed in patients with multiple myeloma treated in similar fashion, clinicians should be aware of this phenomenon we have termed a "melphalan recall" reaction in patients with AL amyloidosis treated with tandem cycles of HDM/SCT.

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### CLINICAL PATHWAYS AND STANDARD OPERATING PROCEDURES: ESSENTIAL TOOLS FOR OUTPATIENT STEM CELL TRANSPLANT PROGRAMS TREATING PATIENTS WITH AL AMYLOIDOSIS

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Clinical pathways (CPs) and standard operating procedures (SOPs) are necessary for treating AL patients with high-dose melphalan and stem cell transplantation (HDM/SCT) in the outpatient setting. AL is a plasma cell dyscrasia in which abnormal proteins

misfold, form fibrils and deposit in vital organs causing malfunction and death. HDM/SCT can produce hematologic remissions and prolong survival. HDM/SCT was developed for the treatment of AL at Boston University Medical Center in 1994. In 1996, treatment was moved to the outpatient setting. The program has been FACT-accredited since 2000. To date, we have performed 496 SCTs. 95% of patients are offered outpatient treatment. While patients with severe cardiac involvement are not candidates for HDM/SCT, patients with less severe cardiac disease can undergo HDM/SCT, with inpatient cardiac monitoring. The CP begins with an extensive multidisciplinary team evaluation involving members from hematology, nephrology, cardiology, pulmonology, neurology, psychiatry, nursing, nutrition, clinical research and the amyloid program. The evaluation involves 3 days of visits which assess organ involvement, performance status, support network including their ability to physically and emotionally adhere to an outpatient treatment program as well as to post-transplant follow-up, and candidacy for a research protocol. Weekly meetings are held to discuss evaluation results and determine eligibility before a patient can be scheduled. Once treatment begins, daily rounds, including toxicity evaluations, physical exams, medication review and reinforcement of the treatment plan are conducted. Oral and written instructions are provided regarding expected toxicities, symptom management and emergency contacts. Prophylactic treatment with antiemetic, antibacterial, antiviral, antifungal and growth factors are used. The most common reason for hospital admission is febrile neutropenia. Severe nausea, vomiting, diarrhea, dehydration may also necessitate hospitalization. CPs and SOPs were developed early on in the program and are adhered to with a mechanism to document any deviations. CPs are reviewed annually for revisions based on current peer-reviewed literature and program experience. Educational short courses are held regularly for staff to insure adherence to CPs and SOPs. In summary, outpatient HDM/SCT is a feasible treatment option for patients with AL amyloidosis, provided treatment is conducted in an experienced center.

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### AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION MAY REVERSE RENAL FAILURE IN PATIENTS WITH MULTIPLE MYELOMA

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**Background:** Approximately 20% of patients with multiple myeloma (MM) have renal failure at diagnosis, and about 5% are dialysis-dependent. These patients may potentially benefit from high-dose chemotherapy and autologous hematopoietic stem cell transplantation (auto SCT). However, many of these patients are considered ineligible for auto SCT due to concerns about increased treatment-related toxicity. We evaluated the outcome of 46 patient with MM and renal failure, defined as serum creatinine  $>2$  mg/dl sustained for  $>1$  month, who received auto SCT at our institution.

**Methods:** Forty-six patients with a median age of 56 years (range: 29–72) received auto SCT between September 1997 and August 2006. Median serum creatinine and creatinine clearance (CrCl) at auto SCT were 2.9 mg/dl (range 2.0 – 12.5) and 33 ml/min (range 8.7 – 63), respectively. Ten patients (22%) were dialysis-dependent.

**Results:** Median follow up in surviving patients was 34 months (range 5–81). Complete (CR) and partial responses (PR) were seen in 9 (22%) and 22 (53%) of the 41 evaluable patients, with an overall response rate of 75%. Two patients (4%) died within 100 days of auto SCT. Grade 2–4 Non-hematological adverse events were seen in 18 patients (39%) and included cardiac arrhythmias, pulmonary edema, hyperbilirubinemia. Median progression-free (PFS) was 22.8 months and median overall survival OS has not yet been reached. Kaplan-Meier estimates of 3-year PFS and OS were 36% and 64%, respectively. Thirty patients (62.5%) are still alive after a median follow up of 34 months, and 18 patients (39%) are alive and progression-free. Significant improvement in renal function, defined as an increase in GFR by 25% above baseline, was seen in 17 patients (37%). None of the 10 dialysis-dependent patients became dialysis independent. A pre-transplant creatinine level of  $\geq 3$ mg/dl

was associated with a significantly shorter overall survival ( $p = 0.05$ , HR 2.8).

**Conclusions:** Auto SCT was safe and feasible in selected patients with MM and renal failure, and was associated with a significant improvement in renal function in approximately one-third of the transplanted patients.

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### CYTOREDUCTIVE REGIMEN CONTAINING RANIMUSTINE (MCNU), CARBOPLATIN, ETOPOSIDE AND CYCLOPHOSPHAMIDE (MCEC) BEFORE AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION (PBSCT) FOR RELAPSED OR REFRACTORY LYMPHOMA

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MCNU, a derivative of nitrosourea that was developed in Japan, shows good penetration into CSF and might be expected to decrease CNS relapse of lymphoid malignancies when used before transplantation. However, its feasibility and efficacy have not been extensively analyzed in adult patients with lymphoma. We retrospectively evaluated an MCEC regimen which consisted of MCNU (200 mg/m<sup>2</sup> on days -8 and -3), carboplatin (300 mg/m<sup>2</sup> on days -7 through -4), etoposide (500 mg/m<sup>2</sup> on days -6 through -4) and cyclophosphamide (50 mg/kg on days -3 and -2) in 68 patients with lymphoma (median age, 48 yr: range, 20–65 yr) who underwent autologous PBSCT at our institution between Jan. 1999 and Feb. 2008. The diagnosis included DLBCL (N = 33), FL (14), including 6 transformants, T-cell lymphoma (12), and HL (9). The median time from diagnosis to PBSCT was 20 months (4–198 mo), and the median number of prior chemotherapy regimens was 3 (2–7). 97% had ECOG PS  $\leq 2$ , 41% had prior XRT, 4% had bulky disease, 62% had stage III-IV disease, 28% had IPI at relapse of H/H-I. The disease status at PBSCT was 1st CR/PR in 15%,  $\geq 2$ nd CR/PR in 72%, and NC/PD in 13%. Grade (G) 4 non-hematological toxicities (CTCAE ver. 3.0) included elevated transaminase (1), hyponatremia (1) and hypokalemia (1). GI and CNS toxicities consisted of G3 mucositis (10), G3 diarrhea (27) and G2 seizure (1). There were no G4 cardiac, pulmonary or renal toxicities except for one who died of treatment-related MOF. The cumulative incidence of relapse at 2 yrs was 49%. Of 33 relapses, 2 occurred newly in the CNS without any previous history. With a median follow-up of 24 months (3–80) after PBSCT for surviving patients, the 2-yr OS and PFS were 68% (95% CI 55–81%) and 50% (95% CI 38–63%), respectively. In univariate analyses, T-cell phenotype ( $p < 0.01$ ), bulky disease ( $p < 0.01$ ), disease status other than CR/PR ( $p < 0.01$ ), stage III-IV ( $p = 0.03$ ), IPI (H/H-I,  $p < 0.01$ ) and treatment without rituximab ( $p < 0.01$ ) were unfavorably associated with OS. Multivariate analysis confirmed that T-cell phenotype (HR 1.85; 95% CI 0.85–2.86,  $p < 0.01$ ), bulky disease (HR 3.02; 95% CI 1.26–4.79,  $p < 0.01$ ), disease status (HR 1.95; 95% CI 0.89–3.01,  $p < 0.01$ ), IPI (HR 2.66; 95% CI 1.19–4.14,  $p < 0.01$ ) and treatment without rituximab (HR 4.12; 95% CI 1.14–7.10,  $p < 0.01$ ) were unfavorably associated with OS. The results suggested that autologous PBSCT with the MCEC regimen is a feasible and effective treatment option for relapsed/refractory lymphoma.

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### TIMING OF HIGH DOSE MELPHALAN (HDM) AND OUTCOMES FOR AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN PATIENTS WITH MULTIPLE MYELOMA (MM)

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HDM is the most widely used preparative regimen for ASCT in MM. The timing of HDM prior to transplantation has varied between studies. HDM is given on day -2 (2 days prior to stem cell infusion) in some and on day -1 in others. At our institution, HDM was initially given on day -2. Considering Melphalan undergoes rapid hydrolysis in plasma with a short half-life in the order of 60–90 minutes, administration on day -1 seemed feasible and